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# Real-world experience using combination therapy with riociguat and risk assessment using REVEAL Lite 2.0 in patients with pulmonary arterial hypertension

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**Abstract**
Pulmonary arterial hypertension is a progressive disease that can lead to right-sided ventricular failure and premature death. Tailoring therapy to individual patient's needs, along with regular risk assessment, is integral for optimal outcomes in patients with pulmonary arterial hypertension. Results from the AMBITION trial support the use of upfront combination of tadalafil and ambrisentan. In a recent analysis of risk assessment in pulmonary arterial hypertension, abridged versions of the REVEAL 2.0 risk score were shown to be comparable to the full tools. In this report, we present a case series of the use of riociguat in upfront combination or sequentially, and the impact on risk scores as determined by the abridged REVEAL Lite 2.0 approach.

**Keywords**
chronic thromboembolic pulmonary hypertension, pulmonary arterial hypertension, pulmonary hypertension, riociguat

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## Introduction

Pulmonary arterial hypertension (PAH) is a progressive disease characterized by elevated pulmonary pressure and increased pulmonary vascular resistance due to vascular proliferation and remodeling of pulmonary arterioles, leading to right-sided ventricular failure and premature death. Tailoring therapy to individual patient's needs, along with regular risk assessment, is integral for optimal outcomes in patients with PAH. While results from the AMBITION trial support the use of upfront combination of tadalafil and ambrisentan,[1] there are reports of other combinations being used as upfront therapy.[2] Recent data supports using objective risk assessment in the evaluation of patients for better outcomes.[3] Riociguat is indicated for the treatment of adults with PAH, to improve exercise capacity and World Health Organization (WHO) Functional Class (FC), and to delay clinical worsening.[4,5] In a recent analysis of risk assessment in PAH, REVEAL Lite 1 and 2, which are abridged versions of the REVEAL 2.0 risk score,[3] were shown to be comparable to the full tools.[6] In this report, we present a case series of the use of riociguat in combination or sequentially, and the impact on risk scores as determined by the abridged REVEAL Lite 2.0 approach.[6] REVEAL Lite 2.0 uses the following variables: renal insufficiency, WHO FC, vital signs, 6-minute walking distance (6MWD), and brain natriuretic protein (BNP) or N-terminal proBNP (NT-proBNP). The six cases are described below.

## Case information

### *Case 1*

This 38-year-old female had no relevant medical history and presented with dyspnea and dizziness. After diagnosis of PAH, initial therapy with riociguat (2.5 mg TID three times daily) and ambrisentan (10 mg QD once daily) was

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**Table 1.** Risk score and other assessments at initial treatment and at follow-up in six patients with PAH.

| | Case 1 | Case 2 | Case 3 | Case 4 | Case 5 | Case 6 |
|---|---|---|---|---|---|---|
| *Values upon initial treatment* | | | | | | |
| Gender/age (yrs) | F/38 | F/57 | M/67 | F/53 | F/77 | M/63 |
| Initial treatment (combination or sequential) | Combination therapy with riociguat (2.5 mg TID) and ambrisentan (10 mg QD) | Combination therapy with riociguat (2.5 mg TID) and selexipag (1600 mcg BID, twice daily) | Riociguat (2.5 mg TID) and macitentan (10 mg QD) | Riociguat (2.5 mg TID), ambrisentan (10 mg QD), treprostinil (1.5 mg BID to TID) | Riociguat (2.5 mg TID) and macitentan (10 mg QD) | Riociguat (2.5 mg BID) and treprostinil |
| FC | II | III | III | II | II | III |
| 6MWD (m) | 383 | 260 | 280 | 440 | 312 | 288 |
| SBP (mmHg) | 124 | 138 | 103 | 115 | 100 | 119 |
| HR (BPM) | 89 | 85 | 66 | 83 | 72 | 80 |
| BNP/NT-Pro BNP (ng/L) | 165 BNP | 126 BNP | 234 BNP | 11 BNP | 210 BNP | 517 BNP |
| eGFR (mL/min/ 1.73 $m^2$) | >90 | 79 | 44 | >90 | 40 | 54 |
| REVEAL 2.0 Lite risk score, after initial therapy | **5** | **7** | **9** | **2** | **9** | **9** |
| Follow-up | Reassessment at 1-year visit | Reassessment at 18-month visit | Reassessment at 20-month visit | Reassessment at around 2 years | Reassessment at 1-year visit | Reassessment at 1-year visit |
| *Values after treatment* | | | | | | |
| FC | II | II | II | II | II | III |
| 6MWD (m) | 462 | 431 | 456 | 485 | 470 | 340 |
| SBP (mmHg) | 117 | 112 | 119 | 114 | 92 | 116 |
| HR (BPM) | 108 | 72 | 54 | 74 | 72 | 69 |
| BNP/NT-Pro BNP (ng/L) | 9 BNP | 72 BNP | 79 BNP | 15 BNP | 305 BNP | 185 BNP |
| eGFR (mL/min/ 1.73 $m^2$) | >90 | >90 | 49 | >90 | 72 | >90 |
| REVEAL 2.0 Lite risk score at follow-up (Change) | **5 (0)** | **5 (−2)** | **5 (−4)** | **2 (0)** | **6 (−3)** | **6 (−3)** |

FC: functional class; BNP: brain natriuretic protein; 6MWD: 6-minute walking distance; eGFR: estimated glomerular filteration rate; HR: heart rate.

started. The patient has been on this combination just over one year, with an increase in 6MWD from 383 m to 462 m and significant improvement in right ventricular (RV) function on echo. Her BNP and 6MWD both improved at year 1 of assessment. The REVEAL Lite 2.0 risk score remained unchanged (Table 1).

### *Case 2*

This 57-year-old female had a history of mixed connective tissue disease, lupus, and Sjögren's syndrome and was referred to the PH clinic with dyspnea and marked limitation in activities of daily living. After confirming diagnosis of PAH, therapy for PAH was initiated with riociguat (2.5 mg TID) and selexipag (1600 mcg BID, titrated over about two months). The patient did well with this combination treatment and improved significantly. The most recent evaluation at 18 months after initiating this combination treatment showed normalization of RV function on echo along with improvement in 6MWD from 260 m to 431 m at 18 months follow-up. Her WHO FC improved from FC III to FC II. The REVEAL Lite 2.0 risk score improved from +7 to +5 after 18 months on the combination treatment (Table 1).

### *Case 3*

This 67-year-old male had a history of liver transplant 10 years prior and was admitted in the ICU with RV failure and massive saddle pulmonary embolism (PE). After recovery from the acute episode, he had persistent elevated PA pressures on follow-up at six months. He was suspected to have chronic thromboembolic pulmonary hypertension (CTEPH) and underwent a CTEPH evaluation, including a pulmonary artery angiogram (PA gram), and was started on riociguat titrated to 2.5 mg TID. His ventilation perfusion scan and PA gram were negative for chronic PE but confirmed PAH. Macitentan was added to riociguat. He did well on this combination and at a 20-month follow-up, he showed sustained improvement from FC III at baseline to FC II. His 6MWD improved from 280 m at diagnosis to 456 m at his 20-month follow-up. The patient had a risk score of +9 at the start of combination therapy and +5 when measured 20 months after starting the combination treatment (Table 1).

### *Case 4*

This is a 53-year-old female with history of Human immunodeficiency virus (HIV) and PAH. She presented at the clinic with dyspnea and peripheral edema and was on a regimen of triple therapy with riociguat 2.5 mg TID, low-dose treprostinil (1.5 mg BID), and ambrisentan (10 mg QD). We increased her oral treprostinil dosage from BID (twice daily) to TID (three times daily) as per the current recommendations. She improved markedly. She continued on the same regimen for the next two years (at the time of writing this report). A repeat right heart catheterization after two years showed improvement in mean pulmonary artery pressure from 50 mmHg (at presentation) to 33 mmHg (at two-year follow-up) and an increase in cardiac index from 1.68 L/min/$m^2$ to 3 L/min/$m^2$, respectively. There was almost complete normalization of RV function on echo at two years after treatment. Her 6MWD increased from 440 m to 485 m at the last evaluation, and the patient reported functional improvement with increased activity levels. The REVEAL Lite 2.0 risk score was unchanged at two-year follow-up (Table 1).

### *Case 5*

This is a 77-year-old female with a history of arthritis and hypercholesterolemia. She presented with dyspnea on exertion, intermittent cough, and chest pressure but no wheezing. She was initially treated with riociguat, titrated to 2.5 mg TID, and improved in her FC but not 6MWD over four months. She was then started on macitentan 10 mg QD. The sequential combination therapy resulted in significant improvement of 6MWD and improvement of REVEAL Lite 2.0 risk score from +9 to +6. RV enlargement did not change throughout the therapy (Table 1).

### *Case 6*

This 63-year-old male had a history of systemic scleroderma, was diagnosed with PAH, and was initially treated with riociguat, titrated to 2.5 mg TID. The patient was FC III and was scheduled for transplant. While awaiting transplant, treprostinil was added to riociguat. The REVEAL Lite 2.0 risk score improved from +9 to +6 after the addition of treprostinil (Table 1).

## Summary

We have described real-world observations of six patients who received initial combination or sequential therapy with riociguat and a prostacyclin analog (PCA) and/or endothelin receptor antagonist (ERA), and the REVEAL Lite 2.0 risk scores associated with each patient after initial treatment and at follow-up. In all cases presented, riociguat was titrated to the maximum dosage of 2.5 mg TID and was well tolerated. Although no prospective study of riociguat in combination with other agents has been conducted, in the pivotal clinical studies for registration, 53% of patients had received pretreatment with an ERA, 10% had received pretreatment with a PCA, and 1% had been treated with an ERA and PCA in combination.[5] Of these six cases, three were at FC III at the initiation of treatment and two improved their FC at subsequent follow-up appointments. Patients who were in FC II at presentation had sustained response as far out as two years, with no decline or addition of therapy while using riociguat in combination as first-line

therapy. Of the six patients, four improved their objective risk assessment score, REVEAL Lite 2.0, and none observed any decline while on the combination therapy including riociguat. Although this is a small observational study, the data supports the upfront use of riociguat for sustained response in combination with other pathway drugs. All patients either maintained their functional status or improved by physician gestalt as well as by objective REVEAL Lite 2.0 assessment. The recently updated American College of Chest Physician guidelines for the management of PAH recommend riociguat combination therapy for patients who remain symptomatic on stable doses of ERA, PCA, or inhaled prostanoid.[7] The current cases show two PH referral centers' real-world experience with riociguat in patients with WHO FC II to III with sustained response on follow-up assessments. Further prospective studies are needed to validate these findings.

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No copyrighted text or trademarked material was used in this report. All ethical procedures were followed in accordance with the preparation of this report. The cases are presented as retrospective view and all patient identifiers have been removed.

## Contributorship

Each author made a substantial contribution to the acquisition, analysis, and interpretation of patient cases. All authors drafted the manuscript and contributed to revisions to ensure cases' accuracy. All authors approved the version to be published.

## Conflict of interest

F.R. is a speaker/consultant for Bayer, Actelion and United Therapeutics. S.S. is a speaker and advisory board consultant with Bayer, Actelion and United Therapeutics. He received a research grant from American College of Chest Physicians.

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